THE PENDING CLAIMS

Claims 1-26 were pending in this application, various claims have been amended, and claim 27 has been added. Accordingly, claims 1-27 remain pending in this application.

THE CLAIM AMENDMENTS

The amendments to the claims to the claims are fully supported by the specification as filed, and by the original claims and, therefore, no objectionable new matter has been introduced within the meaning of 35 U.S.C.§132. Support for the claim amendments is found on page 6, lines 8-17; page 7, lines 17-26; in Example VII, and more specifically lines 25-27 (Claim 1); and page 7 (for the term "diabetes" including all types of diabetes); Examples II to IV (new claim 19) and page 7 (definition of atherosclerotic plaque or lesion"), in claims 1-18 as originally filed; and elsewhere throughout the specification and claims.

THE INDEFINITENESS REJECTION

Claims 1, 3-10 and 19-26 stand rejected under 25USC1.112, second paragraph, as being indefinite.

Claims 1 and 19 have been amended to overcome this ground of rejection.

THE FIRST ANTICIPATION REJECTION

Claim 1 stands rejected under 35 U.S.C. §102(b), allegedly as being anticipated by Levy. This rejection is traversed.

To constitute anticipation under 35 U.S.C.§102, all material elements of a claim must be found in one enabled prior art source. In re Marshall, 577 F.2d 301, 198 USPQ 344 (CCPA 1978); In re Kalm, 378 F.2d 959, 154 USPQ 10 (CCPA 1967).

The examiner's statement that claim 1 "claims a method for treating a disease selected from diabetes mellitus and atherosclerosis ...." is incorrect. Claim 1 has been amended whereas the examiner has copied the same rejection of the previous Office Action. Present claim 1 is directed to a method of reducing insulin and/or glucose plasma levels in a subject afflicted with diabetes by administration of an effective amount of crude Dunaliella powder.

Levy proposed the use of powdered Dunaliella to reduce the susceptibility to oxidation of LDL derived from patients with diabetes mellitus because of their belief that enhanced susceptibility to oxidation of LDL is linked to atherosclerosis. Diabetes and atherosclerosis, however, are separate diseases, and so are their treatments. Diabetes is a disease defined by an increase in blood glucose levels

due to a malfunction in insulin usage by the body. See, attached American Diabetes Association Web Page article. In fact, some studies indicate that the treatment of diabetes may increase the risk of cardiovascular disease.

Levy is different from the claimed invention, and fails to render it obvious. Levy does not treat diabetes mellitus, but refers only to treating atherosclerosis, which is a complication of diabetes. Although Levy uses samples from diabetic patients, nowhere does Levy mention treating diabetes per se. Current claim 1 claims a method of treating diabetes using a crude Dunaliella powder. This is neither disclosed nor suggested by Levy. This rejection should therefore be withdrawn.

In fact, Levy found that the glucose levels of fasting diabetic patients remained unchanged after the treatment. First, Levy provides the mean fasting glucose of the diabetes patients (11.1) and normal control subjects (5.1). See, Levy, at page 55, right hand column, 1st and 3rd paragraphs. Then, when the data are tabulated after treatment, Levy states that "Routine biochemical tests including fasting blood glucose...remained unchanged throughout the study." See, Levy, at page 57, left hand column, 1st. paragraph. This, by itself, renders the Levy reference irrelevant to the presently claimed invention.

In addition, Levy did **in vitro** testing of LDL samples derived from subjects administered carotene, and found improved resistance of LDL to oxidation. Although based on their in vitro data Levy theorized about potential in vivo outcomes, theirs was merely a theory lacking any clinical support. That is, Levy provided no enablement for an in vivo effect of carotene on LDL oxidation. Moreover, subsequent work clearly undermined, and taught away from, Levy's prediction.

Levy's theory was subsequently, but prior to the priority date of this application, found to be in error. Antioxidant supplementation in general, and carotene supplementation in particular, was shown to be ineffective in cardiovascular disease as exemplified below. All references cited herein are of record in this case.

1- Yusaf et al., for example, showed that treatment with an anti-oxidant, such as vitamin E, had no effect on cardiovascular (CV) outcome. See, e.g., Yusaf, S. et al, New England J. Med. (2000), 342:154-60.

2- Kritharides, for example, showed that supplements of vitamin E and -carotene "cannot be recommended" for treatment or prevention of Coronary Heart Disease. See, Kritharides, L., Atherosclerosis (2002) 164:211-21 (Annex D).

3- Zureik et al., for example, showed that supplementation with antioxidant vitamins and minerals had no beneficial effect on carotid atherosclerosis. See, for example, Zureik, M. et al, Arterioscler. Thromb. Vasc. Biol. (2004), 24:1485-1491 (Annex E).

4- Jilal, for example, found that the results of clinical trials employing prospective antioxidant agents were disappointing (page 926, left-hand column, 2nd paragraph), and that the "antioxidant cocktails" have no benefit in the prevention of CVD" (page 928,

left-hand column, 3rd full paragraph). See, for example, Jialal, I, Circulation (2003), 107:926-928 (Annex F).

5- Clarke, for example, found that carotene and vitamin E supplementation showed no protective effect against cardiovascular disease. See, for example, Clarke, R., Cardiovascular Drugs and Therapy (2002), 16:411-415 (Annex G).

6- Hegele, for example, clearly showed that vitamin E supplementation has no effect on cardiovascular outcomes. See, for example, Hegele, R.A., Current Atherosclerosis Reports (2000), 2:361-362 (Annex H).

Clearly, these clinical findings showed an artisan that Levy's findings should be narrowly limited to carotene's improvement of in vitro LDL resistance to oxidation. It is clear from a review of the literature leading to this invention that, contrary to Levy theoretical extension, Levy was wrong as to the clinical effect of carotene on vascular disorders. Levy, thus, not only does not anticipate the present claims, but in fact, Levy's predictions are countered by the subsequent art.

In view of the above remarks, the examiner is invited to withdraw this rejection.

THE SECOND ANTICIPATION REJECTION

Claims 1-2, 8-9, and 16-17 stand rejected under 35 U.S.C. §102(b) as being anticipated by Itoh et al. This rejection is vehemently traversed.

Itoh is different from the claimed invention, and fails to render it obvious. Itoh states that "an increasing tendency of HDL was observed...but **there was no statistically significant difference**". It is clearly seen from Fig. 4 that the difference between treatment with and without Dunaliella is well within the standard deviation (SD). A reference containing data showing a difference that is not statistically significant fails both from a scientific and evidentiary standpoint.

Moreover, although Itoh treated hyperlipidemic patients with Dunaliella (bottom of page 2), the HDL levels of these patients were well within the normal range. The normal range for HDL is defined on page 7 of Itoh as 41-88 mg/dL for females and 41-81 for males. The patients tested had 56-57 mg/dL. See, page 4, 2nd full paragraph of Itoh. **Itoh's administration of Dunaliella to patients with normal LDL levels caused an insignificant increase of HDL**. Current claim 2 claims a method for increasing HDL cholesterol levels in the plasma of a subject in a statistically significant manner, and in need of increasing his/her HDL level. It is well known that it is far more difficult to increase HDL levels in low HDL patients than in normal subjects. See, for example, attached Alsheikh-Ali et al, Atherosclerosis 180:217-223 (2005).

THE FIRST OBVIOUSNESS REJECTION

Claims 1 and 3-10 stand rejected under 35 U.S.C.§103(a), allegedly as being unpatentable over Levy, et al. (U) in view of Beck, Pan et al., Heyman and Smith. This rejection is vehemently traversed. The large number of references needed to establish even an argument for obviousness is clear proof of its failure.

The Levy reference was discussed above, as were the reasons why it fails not only to anticipate but also to render the invention obvious. The combination of Levy with any and all the cited references fails because Levy does not teach treating the disease diabetes mellitus with Dunaliella powder.

Beck is also different from the claimed invention, and fails to cure the deficiencies of Levy. Beck describes the use of bezafibrate for the treatment of normolipidaemic diabetes mellitus type II. According to one aspect of the invention, bezafibrate may be administered as the sole blood glucose-sinking active material. However, insofar as an insulin secretion deficiency is responsible for the diabetes, a parallel administration of insulin releasers may be needed and, if desired, both active materials may be combined in one dosage unit. As insulin releasers, there are preferably used sulphonylureas and especially glibenclamid. Beck teaches nothing about the combination of bezafibrate and crude Dunaliella powder.

Pan, as Beck before, is also different from the claimed invention, and fails to cure the deficiencies of the Levy and/or Beck references. Pan discloses a method for reducing the risk of Type II diabetes by administering a combination of (1) a cholesterol lowering drug such as mevastatin, lovastatin, pravastatin or velostatin, and (2) an angiotensin converting enzyme inhibitor such as captopril, zofenopril, enalapril, ceranapril, fosinopril, lisinopril, fentiapril, pivopril, ramipril, cilazapril, BRL-36,378, MC-838, alacepril, quinapril, indolapril, delapril, spirapril, CGS14,824, CGS16,617, perindopril CI925, and WY-44221. Clearly, Pan teaches a combination of drugs that affect different processes, i.e. a lipid lowering drug and a blood pressure lowering drug while the claimed method requires the combination of activators of nuclear receptors, e.g. cholesterol lowering drugs, with crude Dunaliella powder.

Heyman is also different from the claimed invention, and fails to provide the missing link of the Levy and/or and/or Beck and/or Pan references. Heyman discloses methods and compositions for the treatment of non-insulin-dependent diabetes mellitus using an RXR agonist alone or in combination with a PPAR-γ agonist, e.g. a thiazolidinedione compound. Heyman is silent on combining either an RXR agonist or a PPAR-γ agonist with crude Dunaliella powder.

Smith is also different from the claimed invention, and either alone or in combination with any of the other references fails to render the claimed invention obvious. Smith describes a method for the treatment of diabetes mellitus comprising administering rosiglitazone and insulin. Smith says nothing about combining rosiglitazone with crude Dunaliella powder.

To establish a prima facie case, three requirements must be satisfied.

(1) The prior art must at least suggest all claim limitations. In re Wilson, 424 F.2d 1382, 1385, 165 U.S.P.Q. 494, 496 (C.C.P.A. 1970).
(2) The prior art relied on and the art at the time of the invention must contain some suggestion or incentive that would motivate an artisan to produce a modification. In re Fine, 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988).
(3) The proposed modification must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. Amgen, Inc. v. Chugai Pharm. Co., 927 F.2d 1200, 1209, 18 U.S.P.Q.2d 1016, 1023 (Fed. Cir. 1991).

The above combination of references fails to establish a reasonable expectation of success, when viewed in light of the art as a whole at the time the application was filed. As already indicated above the failure of the combination of the cited references lies fundamentally on Levy's lack of teaching for treating diabetes mellitus, although none of the other references mentions a combination with Dunaliella even as part of a group of products, let alone Dunaliella itself.

In view of the above the examiner is invited to withdraw this rejection.

THE SECOND OBVIOUSNESS REJECTION

Claims 19-26 stand rejected under 35 U.S.C.§103(a), allegedly as being unpatentable over Levy in view of Pan, Craig, Druzgala, and further in view of Boulous. This rejection is also emphatically traversed. The large number of references needed to provide a rejection speaks of the non-obviousness of the claimed invention.

Levy was discussed above as were the reasons for its failure in anticipating and rendering the claimed invention obvious. Levy wanted to treat atherosclerosis and therefore studied LDL oxidation. The fact that they did this in diabetic patients is of no relevance to the claimed invention. Levy reported "unchanged" fasting glucose levels before and after treatment. Levy hypothesized that administering a beta-carotene containing extract of Dunaliella bardawil to diabetic patients will effect a significant reduction in susceptibility to LDL oxidation. Levy employ as a measure of reduction in susceptibility to LDL oxidation an increased lag time and reduction in malondialdehye (MDA) and lipid peroxides (PD). See, e.g., Levy (W), abstract, where it is stated that "Atherogenesis involves oxidative modification of LDL, which is associated with the depletion of the LDL endogenous anti-oxidants," and "Enrichment of LDL with the anti-oxidant .-carotene has the potential of reducing the susceptibility of LDL to lipid peroxidation".

In making this obviousness rejection, the examiner then followed declarant Ami Ben-Amotz and colleagues' reasoning in the Levy articles. That is that anti-oxidants protect LDL against oxidation; that -

carotene contained in Dunaliella acts as an anti-oxidant; and that the administration of the .-carotene in Dunaliella would:

(1) protect LDL from oxidation, and
(2) provide a therapeutic benefit for effectively treating atherosclerosis.
See, e.g. Levy (W), pg. 13, last paragraph.

While the former was demonstrated by Levy and other "early" work discussed below, the latter has been thoroughly disproven by the "later" work also discussed below. The above rejection is based on a hypothesis that was fully discredited and disproven by the filing date of this application. That is that atherogenesis involves LDL oxidation associated with LDL anti-oxidant depletion, and that enrichment of LDL with .-carotene reduces the susceptibility of LDL to lipid peroxidation. The above hypothesis had been shown to be patently erroneous by the intervening art as of September 24, 2003.

"Early" work in this field is exemplified by the articles of Abbey M, Arterioscler. Thromb. (1993), 13:590-600 (Annex B); and Dr. Ben-Amotz' own work, described in Levy, et al., J. Nut. Env. Med. (1995), 5:13-22 (W) and in Levy, et al., Ann. Nut. Metab. 2000, 44(2):54-60 (U). A common thread in these four articles is that they perform in vitro testing of LDL samples derived from patients. No in vivo data was collected or discussed in any of these studies. The in vitro data lead to a prediction of favorable in vivo patient outcomes. It was this prediction of in vivo clinical outcomes, based on in vitro data, that was subsequently proven incorrect.

The "later" work in the field is exemplified by the following articles: Yusaf, S. et al, New England Journal of Medicine (2000), 342:154-60 (Annex C), showing that treatment with an anti-oxidant, such as vitamin E, has no effect on cardiovascular outcomes; Kritharides, L., Atherosclerosis (2002) 164:211-21 (Annex D), which clearly states that supplements of vitamin E and .-carotene cannot be recommended for the treatment or prevention of Coronary Heart Disease; Zureik, M. et al, Arterioscler. Thromb. Vasc. Biol. (2004), 24:1485-1491 (Annex E) which observes no beneficial effects on carotid atherosclerosis of antioxidant vitamin and mineral supplementation; Jialal, I, Circulation (2003), 107:926-928 (Annex F) finds utter disappointment in the results of prospective antioxidant clinical trials (page 926, left-hand column, 2nd paragraph, and further states that it is clear that the antioxidant cocktails have no benefit in the prevention of CVD (page 928, left-hand column, third full paragraph)); Clarke, R., Cardiovascular Drugs and Therapy (2002), 16:411-415 (Annex G) stating that multiple clinical trials failed to show protection against cardiovascular disease (3 large-scale trials of .-carotene supplementation involving 70,000 people and 5 large-scale trials of vitamin E supplementation involving 29,000 patients failed to confirm any protective effect for cardiovascular disease); and Hegele, R.A., Current Atherosclerosis Reports (2000), 2:361-362 (Annex H), showing that vitamin E supplementation had no effect on cardiovascular outcomes.

It is thus apparent that, as of the priority date of this application, it was patently clear that the Levy hypothesis was incorrect. Further, the Levy prediction of .-carotene obtained from crude Dunaliella powder being useful in the therapeutic treatment of diabetes mellitus and atherosclerosis had also been proven wrong. In view that antioxidants lack efficacy in the treatment of cardiovascular diseases, Levy's conclusions would have been disregarded by an artisan in favor of "later" in vivo studies.

Thus, based on the showings that vitamin E and carotene supplementation have "no therapeutic effect" on cardiovascular disease, it would have been expected at the time this application was filed that crude Dunaliella powder "would not have a therapeutic effect" as a result of its anti-oxidant content (the active agent in the crude Dunaliella powder used in the invention is .-carotene). See, for example, paragraph bridging pages 1 and 2 of this application. It was not only neither predictable nor obvious, but counter to the contemporaneous art at the time this application was filed, that crude Dunaliella powder would have an effect on atherosclerosis. It was surprising and unexpected, moreover, that crude Dunaliella powder in fact showed a therapeutic effect as presently claimed.

In summary, as of the priority date of this application, one of ordinary skill in the art would have disregarded Levy (U) and Levy (W) in view of the contemporary showings teaching away from Levy. Levy's disclosures and predictions on the efficacy of treating diabetes mellitus and atherosclerosis with crude Dunaliella powder were considered outdated and in error at the time this application was filed. The claimed invention is thus surprising, unexpected, and counter to the contemporaneous wisdom in the art.

Moreover, the examiner is in error in asserting that LDL levels cause atherosclerosis, as clearly stated by the technical literature. See, for example, Horkko, Free Radical Biology & Medicine, 28:12 1771 (2000). In fact, oxidized LDL prevents atherosclerosis rather than causing it.

Pan was discussed above as were the reasons why it fails to anticipate and rendering the claimed method obvious. Pan discloses a method "for preventing onset of or reducing risk of Type II diabetes, and thereby prevent onset of coronary artery disease and prevent onset of atherosclerosis in mammalian species" (col. 4, lines 27-31). In other words, Pan doesn't teach the prevention of atherosclerosis per se, but rather as a complication of diabetes. By treating diabetes, atherosclerosis is prevented. Furthermore, no experimental data is provided to support the claim of Pan. The invention, on the other hand, teaches a method for treating the disease atherosclerosis without any dependence on its cause.

Craig is also different from the claimed invention, and fails to cure the deficiencies of Levy and/or Pan. Craig discloses the use of a tartrate salt of a thiazolidinedione derivative (rosiglitazone) for the treatment of conditions such as atherosclerosis, which are associated with diabetes. See, page 1, lines 20-22; page 4, lines 19-24 of Craig. In other words, Craig doesn't teach the treatment of atherosclerosis per se, but rather as a condition associated with diabetes. Craig treats diabetes, therefore, improving the

patients risk for atherosclerosis. Furthermore, Craig provides no experimental data to support their hypothesis. The invention, on the other hand, teaches a method for treating the disease atherosclerosis without any dependence on its cause.

Druzgala is also different from the claimed invention, and fails to provide the missing link of its combination with the secondary references. Druzgala discloses the treatment of disorders, such as diabetes, atherosclerosis, hypercholesterolemia, and hyperlipidemia, by administration of a therapeutically effective amount of esterified thiazolidinedione analogs to an individual in need of treatment. Thiazolidinedione compounds include troglitazone, e.g. REZULIN, pioglitazone, and rosiglitazone. Accordingly, Druzgala provides esterified thiazolidinedione analogs and pharmaceutical compositions of these esterified compounds. See, col. 4, lines 31-39 of Druzgala. Clearly, Druzgala relates to analogs of thiazolidinedione and not to the drugs themselves. Druzgala teaches nothing about the combination of thiazolidinedione compounds and crude Dunaliella powder.

Finally, the reliance of the examiner on Boulous is completely without support. Contrary to the examiner's statement, Boulous does not teach a composition comprising lutein, etc., for the treatment of cardiovascular disease. Boulous teaches a composition comprising vitamin E, folic acid, iron, and, optionally, mixed carotenoids. Boulous does not teach the use of Dunaliella to treat atherosclerosis. On the contrary, Boulous states that "the evidence supporting a specific benefit of β-carotene is inconsistent and one large clinical trial suggests an adverse effect". See, page 7 of Boulous.

Furthermore, the examiner is in error in stating that the carotenoids listed in Boulous are "one and the same ingredients shown by Levy to comprise the referenced crude Dunaliella powder". The examiner's statement is apparently based on Levy's statement that "Our HPLC revealed the occurrence of the following carotenoids:...". See, page 56, right hand column of Levy. This Levy statement, however, refers to the analysis of the patients' plasma, and not the analysis of Dunaliella powder. Proof of this is that one of the carotenoids listed is lycopene, which is not contained in Dunaliella powder.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

The combination of the references cited above clearly fails to teach the claimed method. One of ordinary skill in the art would disregard the Levy references for the stated reasons. The applicant is submitting a second Declaration by Shaish (Shaish II Declaration) providing experimental results that clearly show that the combination of crude Dunaliella powder with a PPAR agonist (rosiglitazone) unexpectedly improves the treatment of diabetes when compared with either component alone. The

above, as were the reasons why they fail to suggest the claimed treatment. Claim 2 is directed to a treatment of patients having low levels of cholesterol with crude Dunaliella powder to obtain a statistically significant increase thereof. Nothing in the prior references, nor their combination would have led an artisan to the claimed method.

In view of the above remarks the examiner is once again invited to withdraw this rejection.

CONCLUSION

Based upon the above remarks, the presently claimed subject matter is believed to be novel and patentably distinguishable over the prior art of record. The examiner is therefore respectfully requested to reconsider and withdraw the rejections of claims 1-18 and allow all pending claims presented herein for reconsideration. Favorable action with an early allowance of the claims pending in this application is earnestly solicited.

Respectfully submitted,
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